In The United States Patent and Trademark Office

In Re Patent Application of: Azarlah JOSSIFOFF
Serial No.: 09/856,417
Filed: August 8, 2001
For: VAGINALLY ADMINISTRABLE PROGESTERONE-CONTAINING TABLETS AND METHOD FOR PREPARING SAME
Group Art Unit 1616
Examiner: Alton Pryor

RULE 132 DECLARATION OF AZARIAH JOSSIFOFF

I, the undersigned, Azarlah Jossifoff, of 5 Sapir St., Ramat Gan, Israel, hereby declare as follows:

1. I make this declaration in support of U.S. Patent Application Ser. No. 09/586,417, filed August 8, 2001 (hereinafter "the Application").

2. I received a Ph.D. in pharmacy from Ferrara University in Italy in 1976. I have been a licensed pharmacist in Israel since 1977. During that time I have personally formulated many formulations for different hospitals and clinical researchers, including the Infertility and In Vitro Fertilization (IVF) unit of Sheba Medical Center in Tel Hashomer, Israel (hereinafter "the IVF unit").

3. I was asked by Prof. Jehoshua Dor of the IVF unit to provide a vaginally administrable formulation containing progesterone for use in IVF patients to maintain high progesterone levels in the endometrium of women undergoing IVF treatment. In order to provide such a formulation, I tried several methods:

(a) I tried to formulate 1 g tablets each containing 100 mg of micronized progesterone using a dry compaction method according to the following protocol:

> Mix dry lactose, synthetic cornstarch (i.e. partially pre-gelatinized corn starch sold under the name Starch 1500®), polyvinyl pyrrolidone K-30, magnesium stearate, sodium lauryl sulfate, and micronized progesterone in relative amounts of 70.6 wt%, 15.0 wt.%, 3.0 wt.%, 1.1 wt.%, 0.3 wt.% and 10.0 wt.%, respectively, until the mixture is of uniform composition. Tablet using

appropriate tableting machinery.

The ingredients were mixed using first a planetary mixer and then a double-cone mixer for a total mixing time of about 30 minutes. Except for the micronized progesterone, the ingredients in this protocol were known to be (i) suitable for use in dry compaction processes (for example, the lactose was lactose that had been specially formulated to render it free-flowing), and (ii) non-irritating when administered intravaginally. Using this protocol, I was unable to obtain tablets, because the micronized progesterone was too sticky and insufficiently free-flowing to enable its use in according to the protocol above. Consequently, analysis of the final mixture prior to tableting indicated that it was not possible to obtain a mixture of uniform composition which could be fed to the tabletter for tableting by direct compaction.

(b) I tried to formulate tablets containing 100 mg of micronized progesterone using a dry compaction method using the protocol described in 3(a) above, except that prior to mixing the micronized progesterone with the other ingredients, it was first coated with silica: anhydrous colloidal silica (Aerosil 380) was screened through a #2B screen and then mixed with micronized progesterone for 10 minutes using a double-cone mixer. The ratio of silica to micronized progesterone was about 1:10. The amount of progesterone in each tablet was maintained at 100 mg, and the amount of lactose in each tablet was consequently lowered proportionately to maintain an overall tablet weight of 1 g.

This protocol was based on known protocols in which coating a sticky material with silica and/or mixing with lactose renders the sticky material more free-flowing.

Using this protocol, I was unable to obtain tablets, because despite the silica coating the micronized progesterone remained too sticky and insufficiently free-flowing to enable its use in the protocol described in 3(a) above. *Inter alia*, the micronized progesterone did not mix well with the other ingredients and the

ingredients stuck together in the feed frame, and thus the tablets obtained were not sufficiently uniform in composition to be usable as pharmaceuticals.

(c) I tried to formulate tablets containing 100 mg of micronized progesterone using a dry compaction method, according to the protocol described in 3(a), except that in this protocol, the micronized progesterone was first mixed with an aqueous solution of polyvinylpyrrolidone, and this mixture was then dried and granulated prior to mixing with the remaining ingredients and compacting by dry compaction to form a tablet.

Although tablets were obtained using this method, the tablets obtained were not sufficiently uniform in composition to be usable as pharmaceuticals. This is because the difference between the size of the micronized progesterone/PVP granules was larger than the size of the remaining ingredients, so that mixture of the progesterone/PVP granules with the remaining ingredients yielded an inhomogeneous mixture that resulted in non-uniform tablet composition.

(d) I tried to formulate 1 g tablets containing 100 mg of micronized progesterone using a wet compaction method using the following protocol:

> Lactose monohydrate, corn starch, polyvinyl pyrrolidone and micronized progesterone in relative proportions of 706, 150, 30 and 100 respectively and which had been screened through a # 2B screen were blended in an Erweka double cone blender until a blend of uniform composition was obtained, then wetted with water (125 g water per 1000 grams of other ingredients). The mixture was then dried at 58°C until the humidity content of the mixture approached 0%. The dried material obtained was then granulated using a sieve of 0.875 mm size. The granulated material was then mixed with magnesium stearate and sodium lauryl sulfate, in relative amounts of 11 and 3, respectively. The resulting mixture was fed to a press machine and pressed at a pressure of 12-13 kg/cm^2 into 1 g tablets.

Using this protocol, which is similar to the one described in Example 2 of Greco et al., I obtained tablets of sufficiently uniform composition for use in pharmaceuticals. I supplied the IVF unit with approximately 2000 such tablets for use with its patients. As explained in the declaration of Prof. Dor being filed concomitantly with this declaration, in a significant percentage of patients undergoing in vitro fertilization procedures, the tablets prepared in this way left particulate matter in the vagina or did not dissolve.

(e) The protocol described in 3(d) was repeated, but the relative proportion of corn starch in the tablets was increased to 25 wt.% and the relative proportion of lactose was reduced. I supplied the IVF unit with about 2000 tablets so obtained. As explained in the declaration of Prof. Dor being filed concomitantly with this declaration, in a significant percentage of patients undergoing in vitro fertilization procedures, the tablets prepared in this way left particulate matter in the vagina or did not dissolve.

(f) The protocol described in 3(d) was repeated, but the compression pressure used to press the tablets was reduced to 10 kg/cm^2. It was found that the tablets formed in this way broke apart so easily that they could not be packaged without breakage.

(g) After being informed by Prof. Dor that a significant portion of the tablets formulated per 3(d) above did not dissolve in the patients or left particulate matter in the vagina, I tried to formulate tablets containing 100 mg of micronized progesterone using a direct compaction method, as described in Examples 1 and 2 of the Application. In accordance with this method, the micronized progesterone was first wetted with water and then dried prior to mixing with other ingredients. Unlike the results in 3(c) above, I found that when the micronized progesterone was wetted and then dried alone, as opposed to when it was wetted with another ingredient and then dried as in 3(c), the progesterone was rendered more free-flowing than it had been and that it mixed more readily with the other tablet ingredients. Furthermore, in contrast to the wet granulation method described above and wet granulation methods

generally, following wetting and drying the micronized progesterone did not need to be granulated (sieved) in order to ensure that it would be suitable for mixing with the remaining ingredients of the tablet. The resulting tablets were of acceptably uniform composition to render them suitable for human administration.

Moreover, because the micronized progesterone had been rendered sufficiently free-flowing for use in dry compaction, it became possible to include the ingredients of an effervescent in the tablet. The inclusion of an effervescent was not possible in the tablets produced by the wet-granulation method described in 3(d) above, because the wet conditions would have led to the ingredients of the effervescent reacting with one another and releasing carbon dioxide during the mixing process rather than when inserted into the patient's vaginal area.

I supplied the IVF unit with approximately 2000 tablets containing effervescent formed by this method. I understand from Prof. Dor that in no patients were pieces of the tablets or undissolved tablets been found, as occurred with some of the patients using the tablets prepared as described in paragraph 3(d) above.

4. In view of the results described above, I do not believe that the process described and claimed in the Application is obvious in view of the Greco et al. patents. The step of wetting and drying micronized progesterone prior to mixing the micronized progesterone with the other ingredients, in order to enable direct compaction of the ingredients into a tablet, is neither taught nor suggested by Greco et al. In fact, Greco et al. suggest in Example 14 that forming progesterone-containing tablets by direct compaction will result in tablets which are unsuitable for use for intra-vaginal administration.

5. I also wish to mention that, to the best of my knowledge, the tablets of Greco et al. have never achieved commercial success and were not commerically available as of the filing date of the present application or at any time since. Although I do not know the reasons for this, I can postulate two reasons for this failure. First, wet granulation processes in general involve several steps, which collectively raise the

cost of producing tablets. These steps can be seen in Example 2 of Greco et al.: weighing and measuring ingredients, screening, blending, wetting, drying, subdivision (granulation), remixing, batching and lubrification, and compression. Direct compaction, by comparison, requires only weighing and measuring ingredients, screening, blending and compression, but Greco et al. were unable to produce useable tablets by direct compaction. Second, in view of the experience of the IVF unit using tablets similar to those of Greco et al. prepared by me, it is likely that in some patients the tablets of Greco et al. resulted in the uncomfortable deposition of residual particulate matter, and that Greco et al. were unable to find a way to overcome this difficulty, which the present invention overcomes.

6. In contrast, vaginally administrable progesterone-containing tablets which include an effervescent and which are produced by the method described and claimed in the Application have been approved for human use by the Israel Ministry of Health and are presently sold in Israel under the name Endometrin®. It is my understanding that the IVF unit presently dispenses Endometrin tablets to patients undergoing IVF treatment.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and conjecture are thought to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application of any patent issued thereon.

Azariah Jossifoff, Israel Citizen
5 Sapir St., Ramat Gan, Israel
July 14, 2002

DR. A. Jossifoff.

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RULE 132 DECLARATION OF JEHOSHUA DOR

I, the undersigned, Jehoshua Dor, of No. 2 Yaakov Weiss St., Tel-Aviv, Israel, hereby declare as follows:

1. I make this declaration in support of U.S. Patent Application Ser. No. 09/586,417, filed August 8, 2001 (hereinafter "the Application").

2. I received my M.D. from Tel-Aviv University in 1974. I completed my residency in obstetrics and gynecology (OB/GYN) at Sheba Medical Center in Tel Hashomer, Israel in 1981, where I specialized in reproductive medicine and reproductive endocrinology. I have taught at Sackler Medical School at Tel-Aviv University since 1978, and was made an associate professor in 1993. In 1993 I was a visiting professor at Northshire Hospital in Long Island, New York. Since 1980 I have been affiliated with the Infertility and In Vitro Fertilization (IVF) unit of Sheba Medical Center (hereinafter "the IVF unit"), and have been the head of this unit since 1990. I am a member of several professional societies, and have served as chairman of the Israel Fertility Society since 1999. I was Congress President for the International Congress on Reproductive Medicine, Obstetrics, & Gynecology held in Tel-Aviv in April, 2000.

3. The IVF unit performs approximately 1500 cycles of IVF treatment annually. During my career, I have personally attended to or overseen thousands of IVF treatment cycles. During IVF treatment, administration of progesterone is necessary for implantation of the embryo in the endometrium (the inner lining of the uterus), as progesterone induces in the endometrium the changes that enable the embryo to implant. In principle, such administration may be effected in any one of several different ways. Oral administration of progesterone is the least desirable mode of

administration, because a significant portion of the progesterone administered in this way is rapidly and extensively metabolized in the intestine and the liver, leading to poorly sustained serum levels and low bioavailability. Oral administration of synthetic progesterone-like products, which have similar biological activity to that of progesterone but are not subject to the same drawbacks as progesterone due to metabolism, is limited because of the androgenic activity of these synthetic products. This precludes the sustained use of synthetic progesterone-like products, due to possible teratogenic effects, and thus renders synthetic progesterone-like products unsuitable for use in IVF. Intramuscular injection assures reliable absorption of progesterone, but patient compliance may be low, a fact which may attributed in part to such injections being painful and requiring administration by trained medical personnel. Consequently, vaginal administration of progesterone is considered the most desirable mode of administration.

4. Vaginal administration of progesterone using suppositories or gelatin capsules is known, but not preferred, because the suppositories melt at body temperature, leading to an oily discharge from the vagina, and gelatin capsules (which may also be orally administrable) are difficult to insert into the vagina and require large amounts of progesterone (~600-800 mg per capsule) to achieve the desired effect. At the IVF unit, we tried to get around these problems by using progesterone-containing tablets provided by Azariah Jossifoff, the inventor of the invention which is the subject of the Application. To the best of my knowledge, these tablets were prepared by a wet-compaction method, as described in paragraphs 3(d) and 3(e) of the declaration being filed concomitantly by Mr. Jossifoff in support of the Application. Tablets containing 100 mg progesterone were administered three times a day. Although the rate of successful IVF using these tablets was comparable to the success of IVF using progesterone which was injected intramuscularly, we found that in about 5-7% of the women undergoing IVF treatment, the tablets so prepared did not completely disintegrate, thus leaving particulate matter in the vagina. This was uncomfortable for the women to whom this occurred, and required the attending physician to periodically remove the pieces of tablet which remained in the vagina. Furthermore, in some instances the tablet did not dissolve in the vagina even after several days. The failure to dissolve was usually be detected only after several tablets had been inserted, and resulted in discomfort for the patient. The attending

physician then had to remove the undissolved tablets intact from the patient. In addition to the physical discomfort caused, the failure of the tablets to dissolve meant that the endometrium of the patients in whom this phenomenon was observed did not receive the progesterone required for implantation of the embryos.

5. Subsequently, Mr. Jossifoff began providing the IVF unit with a different form of tablet containing 100 mg progesterone per tablet. It is my understanding that this form of tablet differed from the tablets which were initially provided by Mr. Jossifoff, in that the new tablet was produced by a different process, as described in paragraph 3(g) of Mr. Jossifoff's concomitantly-filed declaration, and contained an effervescent. In hundreds of administrations to patients undergoing IVF using the new tablets, no problems with non-disintegration of tablets or the leaving of residual particulate matter were encountered. The rate of successful IVF using the new tablets equaled or exceeded the rate of successful IVF using the earlier-prepared tablets.

6. The IVF unit presently uses Endometrin® tablets to deliver progesterone to IVF patients. These tablets are approved by the Israel Ministry of Health.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and conjecture are thought to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application of any patent issued thereon.

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